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Comparison of two lumbar manual therapies on temporal summation of pain in healthy volunteers

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Abstract

The purpose of this study was to compare the immediate change in temporal summation of heat pain (TSP) between spinal manipulation (SMT) and spinal mobilization (MOB) in healthy volunteers. Ninety-two volunteers (24 males; 23.8 ± 5.3 years) were randomized to receive SMT, MOB or no treatment (REST) for one session. Primary outcomes were changes in TSP, measured at the hand and foot, immediately following the session. A planned subgroup analysis investigated effects across empirically derived TSP clusters. Primary outcome: There were no differences in the immediate change in TSP measured at the foot between SMT and MOB, however both treatments were superior to the REST condition. Subgroup analysis: The response to a standard TSP protocol was best characterized by three clusters: 52% no change ($n = 48$, 52%); facilitatory response ($n = 24$, 26%), and inhibitory response ($n = 20$, 22%). There was a significant time by treatment group by cluster interaction for TSP measured at the foot. The inhibitory cluster showed the greatest attenuation of TSP following SMT and MOB when compared to REST. These data suggest lumbar manual therapies of different velocities produce a similar localized attenuation of TSP, compared

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Conflict of interest

None declared

Disclosures

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Potential Conflicts of Interest

No conflicts of interest are reported for this study.

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to no treatment. Attenuation of localized pain facilitatory processes by manual therapies was greatest in pain-free individuals who demonstrate an inhibitory TSP response.

Perspective—The attenuation of pain facilitatory measures may serve an important underlying role in the therapeutic response to manual therapies. Identifying patients in pain who still have an inhibitory capacity (i.e. an inhibitory response subgroup) may be useful clinically in identifying the elusive “manual therapy” responder.

Keywords

Spinal manipulation; Spinal mobilization; temporal summation of pain; pain sensitivity; hypoalgesia; randomized controlled trial; cluster analysis; manual therapy

Introduction

Manual therapy applied to the spine is one of several treatments that result in modest clinical improvement for patients. Systematic reviews and meta-analyses commonly combine high-velocity low-amplitude spinal manipulation (SMT) and low-velocity low-amplitude spinal mobilization (MOB) because they are both joint-based techniques.^{13,46,47} However, manual therapists (i.e. clinicians) consider these manual techniques distinctly separate interventions with separate indications and resulting treatment effects. Research comparing the effectiveness of the two techniques on quantitative pain response is limited and the results are conflicting. For example in the treatment of neck pain, Dunning JR et al (2012) found upper cervical and thoracic SMT to be superior to cervical MOB, while Hurwitz EL et al (2002) found both to be equally effective.^{22,33} However whether the mechanisms underlying treatment effects of SMT and MOB are different has not been fully appreciated. If SMT and MOB share the same therapeutic mechanisms then separating the two interventions in clinical trials would serve little purpose.

Numerous specific and non-specific mechanisms underlie clinical improvement in patients with spine pain.^{4,10,12} The immediate attenuation of pain facilitatory measures, as measured by temporal summation of heat pain (TSP), is believed to be a specific underlying therapeutic mechanism of SMT.⁴ The existing literature clearly and consistently demonstrates SMT shows a favorable effect on pain facilitatory processes that exceeds comparative interventions and carefully constructed sham controls.^{7–9,25} For example, in a recently completed randomized controlled trial comparing SMT applied to the lumbar spine to sham-SMT, enhanced sham-SMT and no treatment in 110 participants with LBP, immediate lessening of TSP was only observed in participants receiving the SMT.⁸ In separate parallel studies, pain-free participants (n=60) and those with LBP (n=36) were randomly assigned to receive SMT applied to the lumbar spine, exercise on a stationary bike, or perform low back extension exercises.^{7,25} Lessening of TSP was observed only in participants receiving SMT in both studies. Pain-free volunteers (n=90) have also been randomly assigned to receive SMT to the thoracic spine, neck exercise, or no intervention.⁹ Immediate lessening of TSP was only observed in participants receiving the SMT to the thoracic spine. The body of evidence supports the attenuation of TSP as a specific effect of SMT that may underlie therapeutic benefit.

However this specific mechanism may be shared by other therapeutic interventions, including other manual therapy techniques. Two prior studies have shown that an upper extremity neuromobilization technique, another manual therapy treatment that targets neurovascular structures, also inhibits TSP.^{3,5} Whether or not lessening of pain facilitatory processes is shared by manual therapies has not been fully explored. To our knowledge, no study has compared the immediate effects of two manual therapy techniques, such as SMT and MOB, on TSP.

Recent work suggests that using a fixed thermal heat paradigm to induce TSP in pain-free adults yields substantial variability in response that is not well characterized by group mean response slopes.² Instead, Anderson et al (2013) found that three empirically derived clusters better characterized TSP response slopes. The three distinct clusters were as follows: adults who experienced no change in perceived pain intensity over time (58%), adults who experienced an increase in perceived pain intensity overtime termed ‘a facilitatory response’ (30%) and adults who experience a decrease in perceived pain intensity over time termed ‘an inhibitory response’ (15%). The therapeutic implications of these TSP response groups have not been explored, but have the potential to help better predict how people may respond to treatment before the treatment is applied.

The primary objective of this study was to compare the effects of SMT and MOB on the attenuation of TSP. Based on current theories that suggest a key component of SMT is the high-velocity low-amplitude thrust that is delivered by the therapist, we hypothesized that SMT would demonstrate greater reduction in TSP compared to MOB and a no-treatment control (REST) condition. Support of our hypothesis would suggest a “key” ingredient of SMT affecting TSP is the force by time profile of the intervention. Results supporting the alternative to our hypothesis would suggest that attenuation of TSP may be a shared mechanism across different forms of manual therapies.

In addition, although evidence suggests SMT attenuates TSP, whether the effect is consistent across recently described clusters is unknown. Therefore, a planned subgroup analysis was to compare the immediate reduction in TSP between treatment arms and empirically derived TSP clusters. We theorized that SMT would have the greatest effect on a facilitatory cluster because SMT is an effective treatment for only some patients with low back pain^{46,47} and there are subgroups of patients with low back pain that have enhanced TSP.⁴⁴ In turn, we hypothesized that the attenuation of TSP by SMT would be greatest in the facilitatory cluster.

Methods

Design

This study was a randomized controlled trial consisting of 2 experimental intervention groups and a control arm. Pain-free volunteers, who provided informed consent, completed demographic and pain-related psychological questionnaires, underwent a standardized pain sensitivity assessment, received their assigned intervention, and then completed a second pain sensitivity assessment.

Participants

Volunteers were recruited from the University of Florida and surrounding communities through flyers and listserv approved by the University of Florida's Institutional Review Board (UF IRB). A study representative confirmed eligibility criteria and enrolled appropriate individuals following the guidelines set forth by the UF IRB. Volunteers were eligible if they were between the ages of 18 and 65. Volunteers were ineligible if they were non-English speaking, or reported a systemic medical condition (e.g. diabetes, hypertension), current use of psychiatric medication, pregnant, regular use of prescription or over the counter medication for management of pain, presently experiencing low back pain or other painful condition, or history of surgery to the low back.

Power and Sample Size Estimates

Estimates were made for our primary objectives using data from a prior study performed using an SMT technique applied to the lumbar spine. In that study the between-within interaction in the change score for TSP was $\eta^2=0.12$ ($SD=0.05$).⁷ For this study, a conservative estimate effect size ($\eta^2=0.07$), a 2-tailed null hypothesis, a within session ICC of 0.65 for the primary outcome of TSP¹ and an alpha of 0.05 was used to generate a conservative estimate of power. Thirty participants per treatment group provided greater than 90% power to detect a group x time interaction in the proposed mixed-model. The secondary analysis that compared the treatment effect on TSP across clusters was exploratory.

Randomization

Study volunteers were randomly assigned to one of three groups after completing the baseline evaluation. The randomization scheme was prepared by an individual not involved in data collection of administration of the intervention (MDB), generated by computer and completed prior to the start of the study. Randomized treatment assignments were contained in sealed, opaque, numbered envelopes.

Blinding

Individuals collecting outcome measures and providing the intervention were not blinded. Volunteers were not blinded to the intervention they received.

Intervention

SMT (high-velocity low-amplitude spinal manipulative therapy)—The therapist performed the manipulation technique with the volunteer supine. The therapist stood opposite the side to be manipulated. The participant was passively side-bent away from the therapist. The therapist rotated the participant's torso towards them and then delivered a quick posterior and inferior thrust through the anterior superior iliac spine. This technique has been previously described in the literature and is commonly utilized for the treatment of low back pain.¹⁹ Several randomized trials support the efficacy of this technique and no adverse events have been reported in these trials.^{15,16,23} Additionally, prior studies using this SMT technique have found associated attenuation of pain sensitivity, immediate changes in cortical function and no adverse events.^{7,8,24,25} Participants had the manipulation performed

four times in a 5-minute period because this matches parameters used in clinical situations, as well as prior clinical and mechanistic studies.

MOB (low-velocity low-amplitude spinal mobilization)—The therapist performed a posterior-to-anterior joint mobilization. Volunteers were in the prone (face down) position, contact was made by the therapists' hands at approximately the level of the 3rd lumbar vertebrae (L3) and pressure was applied to spinous process. L3 was identified by first palpating the posterior superior iliac spines and identifying the spinous process in the midline between these bony prominences (in 80% of subjects this is the spinous process of S2) and then moved cranially until the process of L3 was identified. The investigator applied and released a force directed toward the floor, repeating this cycle at a rate of approximately 1Hz for 1 minute three times with a 1-minute rest between cycles.

REST (Control Intervention)—Volunteers randomized to the REST arm (control intervention) rested quietly in the supine position for 5 minutes. Prior studies in healthy subjects suggest that rest has no effect on measures of pain facilitatory processes.^{8,9}

Outcome measures

Pain-related psychological questionnaires—Psychological factors have been shown to influence ratings of experimental pain.^{26,27,31} Subsequently, fear of pain, kinesiophobia, pain catastrophizing, anxiety, and gender role beliefs about pain were collected and post randomization differences between groups were assessed. Psychological factors that differed across groups post-randomization were included as covariates. Fear of pain was assessed with the Fear of Pain Questionnaire (FPQ-III), which uses a 30-item, 5-point rating scale to measure fear about specific situations that would normally produce pain.³⁷ Anxiety was assessed with the State-Trait Anxiety Inventory (STAI), which has 40 items measuring the presence and severity of current symptoms of anxiety and generalized propensity to be anxious.³⁶ Kinesiophobia was assessed with the shortened version of the Tampa Scale of Kinesiophobia (TSK), which has 13 items and has been recommended instead of the original 17-item version for clinical and research purposes.²⁸ Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS), which is a 13-item instrument developed to facilitate research on the mechanisms by which catastrophizing impacts the pain experience in healthy and clinical populations.^{41,52}

Pain Sensitivity Assessment—Volunteers underwent a standardized pain sensitivity assessment that included a behavioral measure of pain facilitatory process. Volunteers were assessed prior to and immediately following the intervention as a measure of immediate effects as per our preliminary studies.^{3–9,25} A computer-controlled device, Medoc NeuroSensory Analyzer TSA-II (TSA-2001, Ramat Yishai, Israel), was used to deliver all thermal stimuli to the skin of participants. Participants received instruction on providing subjective responses of pain intensity using a 101 point numeric pain rating scale (NRS) with 0 indicating “no pain” and 100 indicating the “The most intense pain sensation imaginable” or a 100 mm mechanical visual analog scale (MVAS) anchored with “No pain” and “The most intense pain sensation imaginable”. The use of the NRS or MVAS depended upon the specific QST measure being assessed but always remains consistent. Both the NRS

and MVAS are common for the assessment of pain and demonstrate sound psychometric properties.^{11,20,30,34,35} Before the baseline testing, each subject underwent practice tests to familiarize themselves with the procedures and stimuli (pressure and thermal) that they were to be exposed. In order to standardize the scaling instructions and to clarify the distinction between the sensory intensity and affective dimensions, a standardized instructional set was used for all subjects during every exposure to stimuli. The scale instructions were repeated for every set of ratings within each session.⁴⁵

Pain Sensitivity Testing Sequence—After a practice session where subjects were introduced to the stimuli and rating procedures, the TSP procedure started in either the upper or lower extremity. The starting extremity was randomly assigned. For example if the starting location was the upper extremity, after the sequence of tests were completed, the tests were then completed again in the lower extremity with the same sequence. The pre-intervention starting location was the same as the post-intervention starting location. In addition to TSP static pain sensitivity measures were also collected and post randomization differences between groups were assessed. Static pain sensitivity measures included Heat Pain Threshold (HTH), Supra-Threshold Heat Response (STHR), and Pressure Pain Threshold (PPT). Static pain sensitivity factors that differed across groups post-randomization were included as covariates.

The order of tests was as follows: HTH, STHR, PPT, TSP at location 1; HTH STHR PPT, TSP at location 2; Intervention; HTH STHR PPT, TSP at location 1; HTH STHR PPT TSP at location 2.

Temporal Summation of Pain (TSP)—One block of ten unchanging thermal stimuli were presented quickly one after another. The temperature of each stimulus rapidly fluctuated ($10^{\circ}\text{C.s}^{-1}$) from 39°C to a peak of 50°C , remained at peak temperature for < 1 second, and returned to baseline by active cooling (inter-stimulus interval < 0.33 Hz). Participants were asked by the research assistant, (verbally cued) to rate the magnitude of their “second pain” sensation approximately 1 second after the peak temperature of each heat pulse using the NRS. The 0–100 rating was provided verbally by the participant and was recorded by the research assistant. The change in pain responses over time, from the first to last stimulus is a behavioral measure of pain facilitatory processes. The pain responses are believed to be primarily C-fiber mediated^{42,51} and indicative of endogenous pain facilitatory process.^{43,56} TSP has been calculated several ways, here linear regression was used to calculate an intercept and slope for each subject.² The intercept is representative of an individual's starting value, and the slope is indicative of their change in pain perception over time. The intra-session intraclass correlation coefficient (ICC) for TS calculated in this fashion is good (0.67).¹ TSP measures were taken at 2 anatomical sites. In the upper extremity TSP was assessed on the palmar aspect of the hand on thenar eminence. In the lower extremity TSP was assessed on the arch of the plantar surface of the foot, in the area between ball and heel.

Statistical approach

All statistics were analyzed using IBM SPSS Statistics Data Editor 22 (IBM Corporation, Armonk, NY). The alpha level for statistical significance was set a priori at 0.05. All continuous data were assessed for normality through observation of histograms and with Kolmogorov-Smirnov and Shapiro-Wilk tests. In cases where normality assumptions were not met, assumption-free tests were conducted. All categorical data were assessed with Pearson chi-square or Fisher exact tests. Participants were excluded on a per analysis basis when there was incomplete data for that particular analysis. Descriptive statistics were calculated for demographic variables. One-way ANOVAs were calculated on all baseline measures to determine if there were post-randomization differences.

Primary Outcome—Treatment effects on pain sensitivity measures were examined using mixed-model ANOVAs with time (pre-intervention, post-intervention) as the within-subject factor and randomized treatment group as the between-subject factor. The main effect of time and the interaction between time and treatment were tested. Separate models were constructed for the slope of TSP (i.e. rate of summation), intercept of TSP (i.e. starting rating), HTH, STHR, and PPT at the hand and foot. When Mauchly's Test was significant beyond the 0.05 level, a Huynh-Feldt degrees of freedom correction was employed.

Subgroup Analysis—To establish empirically derived TSP response clusters, a hierarchical cluster analysis (using Ward's method and a squared Euclidian distance measure interval) was performed on the combined (hand and foot) baseline TSP (i.e. slope) data in order to identify homogenous subgroups. The appropriate cluster solution was determined by calculating the percentage change between the clusters (i.e. the "step change"). The point at which the percentage change is significantly larger than that of the previous steps indicates that dissimilar clusters have been merged, and thus suggests the optimal solution.²⁹ Comparisons were made to prior empirically derived clusters in healthy adults.²

Comparison of treatment effects on TSP across clusters was examined using mixed-model ANOVAs with time (pre-intervention, post-intervention) as the within-subject factor and randomized treatment group and TSP cluster as the between-subject factors. Separate models were constructed for TSP (i.e. slope), at the hand and foot. The following effects were tested: 1) the main effect of time, 2) the two-way interaction between time and cluster, 3) the two-way interaction between time and treatment, and 4) the three-way interaction between time, cluster, and treatment. When Mauchly's Test was significant beyond the 0.05 level, a Huynh-Feldt degrees of freedom correction was employed. Effects sizes were calculated between all pairwise treatment group combinations and are reported in Cohen's d. In the sub analysis, effect sizes were calculated between all pairwise treatment combinations within each cluster. Interpretation of the scores are as follows: The effect size was calculated based on the mean pre-post change in the treatment group minus the mean pre-post change in the control group, divided by the pooled pretest standard deviation. Although previous research has recommended several measures of effect size for studies with repeated measurements in both treatment and control groups, the chosen method was favored in terms of bias, precision and robustness to heterogeneity of variance.⁴⁰ The downside to this approach is that the pre-post-tests are not treated as repeated measures but as independent

data. This results in a more conservative estimate of the treatment effect, and debate continues over the “best” method.

Results

A total of 92 healthy volunteers met eligibility criteria, were enrolled into the study, and provided data for these analyses. All subjects completed the study. Table 1 includes information on demographics for each treatment group. Post randomization comparisons between treatment groups indicated no differences for demographic, psychological, or static pain sensitivity variables ($P > 0.05$) (TABLE 1). No adverse events were reported.

Primary Outcome - Effects of treatment on TSP

In the lower extremity (i.e. foot), the treatment by time interaction was significant, suggesting the effect of time was dependent on treatment ($F_{(2,85)} = 3.45$, $p = 0.03$) (TABLE 2). The two treatment arms (SMT mean difference = -0.43 , 95% CI = $[-1.03, 0.17]$; MOB mean difference = -0.32 , 95% CI = $[-0.94, 0.30]$) showed an attenuation effect when compared to the change overtime in the control group (REST mean difference = 0.59 , 95% CI = $[-0.01, 1.19]$) (FIGURE 1). The effect of SMT and MOB differed from the control group but not from each other. The effect size, comparing each treatment to one another, is presented in Table 3. The main effect of time for slope was not significant, suggesting that the average change in TSP across all subjects (including controls) was not greater than zero (main effect of time, $F_{(1,85)} = 0.08$, $p = 0.77$).

In the upper extremity (i.e. palm), the main effect of time and the interaction between time and treatment were non-significant for slope, suggesting that TSP measured in the upper extremity did not change over time and there was no treatment effect ($p > 0.05$). At both anatomical locations, the main effect of time and the interaction of treatment x time for the intercept (i.e. rating of the initial heat stimulus) was non-significant, suggesting the initial rating of the heat stimulus did not vary over time and there was no treatment effect ($p > 0.5$).

Secondary Outcomes: Static Heat and Pressure Pain Sensitivity

The immediate effects of SMT and MOB on HTH, STHR, and PPT measured in the upper and lower extremities were non-significant ($p > 0.05$) (Supplemental TABLE 1).

Cluster Analysis - TSP subgroups

The cluster analysis explored whether baseline TSP, i.e. the change in pain perception to repetitive stimuli could be separated into distinct subgroups. Examination of the agglomeration coefficients for the hierarchical cluster analysis suggested the optimum number of TSP clusters was three (TABLE 4). The majority ($n = 48$, 52%) of our sample fell in the no change subgroup (mean slope = 0.08 , standard deviation = $0.$), meaning that the perception of pain did not change to repetitive stimuli. In 26% of the sample there was a perception of increasingly greater pain evoked by each stimulus (facilitatory subgroup, $n = 24$, mean slope = 1.92 , standard deviation = 1.00). In the remainder 22% of the sample, the perception of pain decreased over the course of 10 stimulus, (inhibitory subgroup, $n = 20$, mean slope = -1.83 , standard deviation = 0.75) (FIGURE 2). Our findings are consistent

with results of the previous cluster analysis of TSP subgroups measured in healthy participants.² Demographic, psychological and pain sensitivity measures separated by cluster are presented in Table 5. Significant differences in fear of pain ($p < 0.05$), specifically fear of medical pain and severe pain, were observed across TSP clusters. The inhibitory subgroup had lower fear of pain compared to the facilitatory subgroup, while the no change subgroup was not different from the others.

Subgroup Analysis - Effects of treatment based on TSP cluster

To test whether the treatment effects observed in the primary analysis was consistent across all subgroups, a repeated measures ANOVA was conducted. Slope measured at the foot was the only outcome measure demonstrating significant treatment effects, and therefore was the dependent measure in this secondary analysis. The independent factors were main effect of time, which had two levels “pre-treatment” and “post-treatment”; interaction effect between cluster, which had three levels “no change”, “facilitatory”, and “inhibitory”, x time; interaction effect between treatment group, which had three levels, x time; and the three-way interaction between time, cluster, and treatment group.

The three-way interaction (time x treatment group x TSP cluster) was significant, suggesting the effect of time across TSP clusters were dependent on treatment group ($F_{(4,79)} = 2.52$, $p = 0.05$, partial $\eta^2 = 0.11$) (TABLE 6). To decompose the three-way interaction, the mean difference in slope was estimated for each treatment nested within the TSP Clusters (FIGURE 3A–C). In the inhibitory subgroup the slope of TSP was attenuated by SMT and MOB compared to the REST condition (FIGURE 3A). The treatment effect in this cluster was similar to the average treatment effect across the sample. The effect of SMT and MOB was similar to the REST condition within the no change and facilitatory subgroup (FIGURE 3B & C). Within each subgroup the effect size of each intervention in comparison to one another is presented in Table 3.

Discussion

Primary Outcome

We used healthy adults to examine the comparative effects of SMT and MOB on TSP measured at two anatomical locations, the hand and foot. We found no evidence that the immediate effect on TSP assessed at the foot differs when a joint-biased manual therapy is applied at different velocities (i.e. high-velocity and low-velocity). However, compared to the no-treatment REST condition, SMT and MOB demonstrated a similar attenuation effect on TSP. We did not observe a treatment effect on TSP assessed at the hand, suggesting that the effect is localized. Our findings do not support our primary hypothesis that SMT would have a greater attenuation of TSP than MOB and REST. Our prior work has demonstrated SMT’s favorable effect on TSP that exceeds comparative interventions and carefully constructed sham controls. This is the first study to demonstrate SMT and MOB result in a similar attenuation of pain facilitatory measures, as measured by TSP. This finding provides support for a conceptual model where joint-based manual therapies (i.e. SMT and MOB) engage similar central nervous system (CNS) mechanisms that underlie therapeutic benefit. The attenuation of TSP has been observed following another form of manual therapy that

does not target the joint, specifically upper extremity neurodynamic techniques.^{3,5} The results of these studies combined with the results of the current study supports the hypothesis that similar CNS responses may be a consequence of various forms of manual therapy that may underlie their analgesic effect.

The attenuation of TSP by manual therapy may be mediated by several CNS mechanisms. The effect of manual therapy on TSP in this study was only observed in the foot and not the hand. The localized effect may be related to the location of the spine where the treatment is applied. Prior studies of SMT applied to the lumbar spine observed changes in TSP assessed at the foot, however those studies did not assess TSP assessed in other locations. Changes in TSP assessed in the hand have been observed following SMT, however in that study, SMT was applied to the thoracic spine. In our study, SMT and MOB were applied to the lumbar spine and the localized effect may point to the spinal cord as an area where CNS modulation occurs. Effects taking place within the spinal cord following spinal manipulation and mobilization have been previously reported. For example in an animal model, joint mobilization of the knee resulted in dermatome specific hyposalgesia that was mediated through descending modulatory activity in the spinal cord.^{48,49} Moreover, ventral horn motor neuron excitability in the lumbar spine is reliably attenuated following SMT applied to the lumbar spine in human subjects.²¹ Recent studies employing functional magnetic resonance imaging (fMRI) have observed supra-spinal changes following manual therapy. The blood-oxygen-level-dependent (BOLD) signal associated with a painful pressure stimulus is reduced in several cortical regions following thoracic SMT. Following the thoracic SMT, there was also a reduction in the intensity of pain associated with the pressure stimulus which was correlated with reduced BOLD signal in the insular cortex.⁵⁰ Changes in resting-state functional connectivity (rsFC) have also been observed following manual therapy applied to the lumbar spine. Reductions in rsFC between the primary somatosensory cortex and posterior insular cortex and increased rsFC between the anterior insular cortex and periaqueductal grey were found immediately following treatment. However, further research is needed to disentangle the extent to which these CNS changes are unique and specific to manual therapy versus shared CNS mechanisms associated with analgesic treatments, including placebo analgesia.²⁴

TS Subgroups

The empirically derived TSP clusters were similar to those reported by Anderson et al (2013) and suggest this method may be a robust way to classify TSP into distinct profiles. The propensity of an individual to experience amplified pain with repeated stimuli is associated with the balance between ascending and descending nociceptive processing, where heightened ascending nociceptive processing is associated with a greater TSP.¹⁴ Brain imaging may be useful in future work to identify the central mechanism by which TSP is reduced following a treatment such as SMT. Brain imaging may be able to assess the direction of the shift in the balance between anti and pro nociceptive processing.

In this study TSP was calculated using linear regression of an individual's 10 VAS responses. However, TSP has been estimated using alternative calculations such a high-response minus baseline, response to the 5th pulse minus baseline, and response to the 10th

pulse minus baseline.² An individual's response profile would differ using alternative calculation methods. For example, no individual would show an inhibitory profile using the high-response minus baseline, while we reported that approximately 22% of healthy individuals show a negative linear trend to a fixed temperature TSP protocol. The within-session reliability of TSP calculated in several ways has been previously reported with the most reliable approach being the one used in this study (i.e. linear regression).¹

When all profiles are combined, SMT and MOB attenuate TSP to a greater extent than rest; however, the results of our sub analysis suggest these effects are more pronounced in the 'inhibitory' TSP cluster. These results were contrary to our hypothesis that the attenuation of TSP by SMT would be greatest in the facilitatory cluster, because they would have the most "room for improvement" and because there are subgroups of patients with back pain, neck pain, and whiplash that demonstrate enhanced pain facilitation (i.e. greater TSP).³⁹

The clinical benefits of SMT have been hypothesized to be exerted through normalization of enhanced pain facilitation. However, our results suggest that these interventions may help individuals that are already inclined to inhibit. We believe these findings suggest manual therapy works best to reduce central excitability by enhancing inhibition in individuals who already have strong central inhibitory pathways. Based on the results of our sub analysis, we would predict that clinical patients with an 'inhibitory' TSP cluster would have a greater neurophysiological and clinical response to SMT compared to a 'facilitatory' TSP cluster. Successfully identifying this 'subgroup' may increase the effects (and effect sizes) of manual interventions for spine pain. Our results support recent findings that showed individuals with spinal pain and high pain sensitivity and elevated TSP have less clinical improvement following a two-week course of manual therapy than other pain sensitivity clusters.¹⁷ These findings point towards the possibility of elevated TSP being a prognosticator of a poor treatment response. This possibility is counter-intuitive as "normalizing" elevated TSP was suggested as an underlying therapeutic mechanism, based on the large body of evidence demonstrating SMT attenuates TSP. Our findings may also help to explain the smaller effects for chronic pain conditions versus acute pain conditions, if we assume that acute pain samples are likely to have higher concentrations of people with inhibitory potential.

Limitations

There are limitations in this study to consider. This study enrolled pain-free adults and compared effects of SMT to MOB on TSP. Therefore caution is needed when extrapolating comparable effects will be observed between SMT and MOB in a clinical sample of patients with pain. Currently, there is limited evidence suggesting the effect size of manual interventions on pain sensitivity differs between clinical and non-clinical populations,^{18,38}, however TSP was not studied.

In this study we employed a fixed peak temperature of 50°C in our methodology to evoke TSP. This methodology induces a highly variable amount of TSP across individuals. An alternative TSP methodology would be an individualized peak temperature to induce a specific amount of amplification (i.e. slope) in each individual. Using the alternative methodology two outcomes could be employed: 1) changes in the peak temperature to

induce the same amount of TSP as baseline or 2) the reduction of TSP (i.e. slope) from a baseline value that is similar across individuals. In the first alternative outcome, an increase in peak temperature following an intervention would be interpreted as a reduction in central sensitization (i.e. positive response), while in the second alternative outcome a decrease in TSP would be considered a positive response. The methodology used in this study is consistent with the prior studies investigating the effects of SMT on TSP. Future research on the effects of SMT on TSP may wish to consider alternative methodologies to evoke TSP since so few individuals demonstrated a greater perception of pain with repeated heat pain stimuli. The immediate change in this measure following treatment might be different if each individual's baseline level of TSP was similar.

The outcome in this study was a hypothesized mechanism of action and not a clinical measure such as pain and disability. Although TSP is associated with clinical outcomes in individuals with spinal pain³² the link between immediate changes in neurophysiological measures and changes in clinical outcomes needs further clarification. As such, concluding clinical equivalence between the treatments is beyond the scope of this study. Future work is needed to elucidate the utility of these neurophysiological measures as a therapeutic mechanism, clinical predictor, and predictor of treatment response.

We did not blind participants from the interventions they received and cannot control for participant bias of receiving or not receiving hands-on therapy. We did not blind the interventionists or assessor and cannot control for potential bias. Further we did not control for subjects' expectation, which can influence the immediate effect of SMT on TSP.⁶ Despite these limitations we are encouraged that our subgroup analysis identified that differences in response to interventions was based on subgrouping of pain sensitivity responsiveness.

Conclusion

The attenuation of pain facilitatory measures may serve an important underlying role in the therapeutic response to manual therapies. In this study we did not find evidence that there were differences in the immediate change in TSP between SMT and MOB, however both treatments showed a greater attenuation compared to the REST condition. This result suggests that lessening of pain facilitatory processes is a shared mechanism by manual therapies. In the elusive search for the "manual therapy responder", the results of our sub analysis that targeting patients with enhanced pain facilitation may not be the way to go. The results from this preclinical trial suggest that targeting patients who still have an inhibitory capacity (i.e. an inhibitory response subgroup) may be more promising.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Alappattu MJ, Bishop MD, Bialosky JE, Goerge SZ, Robinson ME. Stability of behavioral estimates of activity-dependent modulation of pain. *J Pain Res.* 2011; 4:151–157. [PubMed: 21811390]
2. Anderson RJ, Craggs JG, Bialosky JE, Bishop MD, George SZ, Staud R, Robinson ME. Temporal summation of second pain: variability in responses to a fixed protocol. *Eur J Pain.* 2013; 17:67–74. [PubMed: 22899549]
3. Beneciuk J, Bishop MD, George SZ. Effects of upper extremity neural mobilization of thermal pain sensitivity: a sham controlled study in asymptomatic participants. *JOSPT.* 2009; 39:428–438. [PubMed: 19487826]
4. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther.* 2009; 14:531–8. [PubMed: 19027342]
5. Bialosky JE, Bishop MD, Price DD, Robinson ME, Vincent KR, George SZ. A randomized sham-controlled trial of a neurodynamic technique in the treatment of carpal tunnel syndrome. *JOSPT.* 2009; 59:709–723.
6. Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. *BMC Musculoskelet Disord.* 2008; 9:19. [PubMed: 18267029]
7. Bialosky JE, Bishop MD, Robinson ME, Zeppieri G Jr, George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Phys Ther.* 2009; 89:1292–1303. [PubMed: 19797305]
8. Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *J Pain.* 2014; 15:136–48. [PubMed: 24361109]
9. Bishop MD, Beneciuk JM, George SZ. Immediate reduction in temporal summation after thoracic spinal manipulation. *Spine J.* 2011; 11:440–446. [PubMed: 21463970]
10. Bishop MD, Torres-Cueco R, Gay CW, Lluch-Girbes E, Beneciuk JM, Bialosky JE. What effect can manual therapy have on a patient's pain experience? *Pain Manag.* 2015; 5:455–64. [PubMed: 26401979]
11. Bolton JE, Wilkinson RC. Responsiveness of pain scale: a comparison of three pain intensity measures in chiropractic patients. *J Manipulative Physiol Ther.* 1998; 21:1–7. [PubMed: 9467094]
12. Bolton PS, Budgell BS. Spinal manipulation and spinal mobilization influence different axial sensory beds. *Med Hypotheses.* 2006; 66:258–62. [PubMed: 16242852]
13. Bronfort G, Haas M, Evans RL, Mouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. *The Spine Journal.* 2004; 4:335–356. [PubMed: 15125860]
14. Chen JC, Erpelding N, Kucyi A, DeSouza DD, Davis K. Individual differences in temporal summation of pain reflect pronociceptive and antinociceptive brain structure and function. *J Neurosci.* 2015; 35:9689–700. [PubMed: 26134651]
15. Childs JD, Fritz JM, Flynn TW, Irrgang JJ, Johnson KK, Majkowski GR, Delitto A. A clinical prediction rule to identify patients with low back pain most likely to benefit from spinal manipulation: a validation study. *Ann Intern Med.* 2004; 141:920–8. [PubMed: 15611489]
16. Cleland JA, Fritz JM, Kulig K, Davenport Tem Eberhart S, Magel J, Childs JD. Comparison of the effectiveness of three manual physical therapy techniques in a subgroup of patients with low back pain who satisfy a clinical prediction rule: a randomized clinical trial. *Spine.* 2009; 34:2720–2729. [PubMed: 19940729]
17. Coronado RA, Bialosky JE, Robinson ME, George SZ. Pain sensitivity subgroups in individuals with spine pain: potential relevance to short-term clinical outcomes. *Phys Ther.* 2014; 94:1111–22. [PubMed: 24764070]
18. Coronado RA, Gay CW, Bialosky JE, Carnaby GD, Bishop MD, George SZ. Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis. *J Electromyogr Kinesiol.* 2012; 22:752–67. [PubMed: 22296867]

19. Delitto A, Erhard RE, Bowling RW. A treatment-based classification approach to low back syndrome: identifying and staging patients for conservative treatment. *Phys Ther.* 1995; 75:470–485. [PubMed: 7770494]
20. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg.* 1998; 68:102–6.
21. Dishman JD, Weber KA II, Corbin RL, Burke JR. Understanding inhibitory mechanisms of lumbar spinal manipulation using the H-reflex and F-wave responses: A methodological approach. *H-Reflex J Neurosci Methods.* 2012; 210:169–77. [PubMed: 22878176]
22. Dunning JR, Cleland JA, Waldrop MA, Arnot CF, Young IA, Turner M, Sigurdsson G. Upper cervical and upper thoracic thrust manipulation versus nonthrust mobilization in patients with mechanical neck pain: a multicenter randomized clinical trial. *JOSPT.* 2012; 42:5–18. [PubMed: 21979312]
23. Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, Butler B, Garber M, Allison S. A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. *Spine.* 2002; 27:2835–2843. [PubMed: 12486357]
24. Gay CW, Robinson ME, George SZ, Perlstein WM, Bishop MD. Immediate changes after manual therapy in resting-state functional connectivity as measured by functional magnetic resonance imaging in participants with induced low back pain. *J Manipulative Physiol Ther.* 2014; 37:614–627. [PubMed: 25284739]
25. George SZ, Bishop MD, Bialosky JE, Zeppieri G Jr, Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskelet Disord.* 2006;7–86. [PubMed: 16448572]
26. George SZ, Dannecker EA, Robinson ME. Fear of pain, not pain catastrophizing, predicts acute pain intensity, but neither factor predicts tolerance or blood pressure reactivity: An experimental investigation in pain-free individuals. *Eur J Pain.* 2005; 5:457–465.
27. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *J Pain.* 2007; 8:2–10. [PubMed: 17207739]
28. Goubert L, Crombez G, Van Damme S, Vlaeyen JW, Bijttebier P, Roelofs J. Confirmatory factor analysis of the Tampa Scale of Kinesiophobia: invariant two-factor model across low back pain patients and fibromyalgia patients. *Clin J Pain.* 2004; 20:103–10. [PubMed: 14770050]
29. Hair, JF., Balck, WC., Babin, BJ., Anderson, RE., Tatham, RL. *Cluster Analysis.* 6. Vol. Chapter 8. New York: Macmillan Publishing Company; 2006. *Multivariate Data Analysis.*
30. Hartick CT, Kovan JP, Sharpior S. The numeric rating scale for clinical pain measurement: a ratio measure? *Pain Pract.* 2003; 3:310–6. [PubMed: 17166126]
31. Hirsh AT, George SZ, Bialosky JE, Robinson ME. Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *J Pain.* 2008; 9:806–12. [PubMed: 18486557]
32. Hubscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. *Pain.* 2013; 154:1497–504. [PubMed: 23711482]
33. Hurwitz EL, Morgenstern H, Harber P, Kominski GF, Yu F, Adams AH. A randomized trial of chiropractic manipulation and mobilization for patients with neck pain: clinical outcomes from the UCLA neck-pain study. *Am J Public Health.* 2002; 92:1634–41. [PubMed: 12356613]
34. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain.* 2003; 4:2–21. [PubMed: 14622723]
35. Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain.* 1992; 83:157–62.
36. Julian LJ. *Measure of Anxiety.* *Arthritis Care Res.* 2011
37. McNeil DW, Rainwater AJ 3rd. Development of the Fear of Pain Questionnaire – III. *J Behav Med.* 1998; 21:389–410. [PubMed: 9789168]
38. Millian M, Leboeuf-Yde C, Budgell C, Anorim MA. The effect of spinal manipulative therapy on experimentally induced pain: a systematic literature review. *Chiropr Man Therap.* 2012; 20:26.

39. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther.* 2010; 15:135–41. [PubMed: 20036180]
40. Morris SB. Estimating Effect Sizes From Pretest-Posttest-Control Group Designs. *Organizational Research Methods.* 2008; 11(2):364–386.
41. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neil E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med.* 1997; 20:589–605.
42. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain.* 2002; 99:49–59. [PubMed: 12237183]
43. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain.* 2009; 144:16–9. [PubMed: 19359095]
44. Rabey M, Slater H, O'Sullivan P, Beales D, Smith A. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain.* 2015; 156:1874–84. [PubMed: 26020225]
45. Rosier EM, Iadarola MJ, Coghill RC. Reproducibility of pain measurement and pain perception. *Pain.* 2002; 98:205–16. [PubMed: 12098633]
46. Rubinstein SM, Terwee CB, Assendelft WJJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for acute low back pain: an update of the Cochrane review. *Spine.* 2013; 38:E158–E177. [PubMed: 23169072]
47. Rubinstein SM, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: An update of a Cochrane review. *Spine.* 2011; 36:E825–E846. [PubMed: 21593658]
48. Skyba DA, Radhakrishnan R, Rohlwing JJ, Wright A, Sluka KA. Joint manipulation reduces hyperalgesia by activation of monoamine receptors but not opioid or GABA receptors in the spinal cord. *Pain.* 2003; 106:159–68. [PubMed: 14581123]
49. Sluka KA, Skyba DA, Radhakrishnan R, Leeper BJ, Wright A. Joint mobilization reduces hyperalgesia associated with chronic muscle and joint inflammation in rats. *J Pain.* 2006; 7:602–74. [PubMed: 16885017]
50. Sparks C, Cleland JA, Elliott JM, Zagardo M, Liu WC. Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *JOSPT.* 2013; 43:340–348. [PubMed: 23485766]
51. Staud R, Price DD, Fillingim RB. Advanced continuous-contact heat pulse design for efficient temporal summation of second pain (windup). *J Pain.* 2006; 7:575–82. [PubMed: 16885014]
52. Sullivan MJL, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess.* 1995; 7:432–524.
53. Van Damme S, Crombez G, Bijttebier P, Goubert L, Van Houdenhove B. A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain.* 2002; 3:319–324.
54. Walton DM, Levesque L, Payne M, Schick J. Clinical pressure pain threshold testing in neck pain: comparing protocols, responsiveness, and association with psychological variables. *Physical Therapy.* 2014; 94:827–837. [PubMed: 24557645]
55. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 2011; 152:S2–15. [PubMed: 20961685]
56. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol.* 2010; 23:611–5. [PubMed: 20543676]

Highlights

- SMT and MOB equally attenuate TSP compared to no treatment.
- In pain-free individuals, variability in TSP is best explained by 3 subgroups.
- The magnitude of the effect size of SMT on TSP differs across TSP subgroups.

FIGURE 1.

Main Treatment Effect

* - Changes in TSP are significantly different from control

Error Bars represent 95% confidence intervals

FIGURE 2.
Cluster Analysis - TSP subgroups

FIGURE 3 A

FIGURE 3 B

FIGURE 3 C

FIGURE 3.

FIGURE 3A: Treatment Effect within Cluster 3 ‘Inhibitory Subgroup’

* - Changes in temporal summation are significantly different from control

Error Bars represent 95% confidence intervals

FIGURE 3B: Treatment Effect within Cluster 1 ‘No Change Subgroup’

* - Changes in TSP are significantly different from control

Error Bars represent 95% confidence intervals

FIGURE 3C: Treatment Effect within Cluster 2 ‘Facilitatory Subgroup’

* - Changes in TSP are significantly different from control

Error Bars represent 95% confidence intervals

Table 1

Sample Baseline Characteristics

Variable	Sample (N=92)	SMT (N=32)	MOB (N = 30)	REST (N = 30)	p-value post-randomization differences
Gender	24 (26.1%) Male	5 (15.6%)	8 (26.6%)	11 (36.6%)	0.17
Age	23.8 (5.3)	23.7 (4.9)	24.3 (6.8)	23.5 (4.2)	0.85
H-Thres Arm	45.0 (2.8)	44.5 (2.8)	44.8 (2.9)	45.7 (2.6)	0.18
P-Thres Arm	24.8 (10.5)	23.9 (11.2)	24.4 (9.8)	26.3 (10.6)	0.65
H-Thres Leg	45.4 (2.6)	44.9 (2.5)	45.3 (2.4)	46.1 (2.8)	0.18
P-Thres Leg	32.8 (12.5)	32.0 (11.4)	33.7 (13.3)	32.8 (13.3)	0.87
TS Intercept Arm	41.3 (24.8)	46.7 (25.4)	43.3 (26.8)	33.5 (20.6)	0.10
TS Slope Arm	-0.35 (1.7)	-0.25 (1.7)	0.00 (1.7)	-0.81 (1.5)	0.16
TS Intercept Leg	29.4 (20.1)	27.3 (17.5)	36.0 (24.3)	25.0 (16.8)	0.08
TS Slope Leg	0.15 (1.5)	0.55 (1.5)	0.18 (1.6)	-0.31 (1.3)	0.07
FPQ Total	76.6 (14.1)	78.4 (14.2)	77.1 (15.1)	74.3 (13.1)	0.51
FPQ-Minor	18.0 (4.6)	18.2 (4.5)	19.3 (5.0)	16.5 (4.0)	0.06
FPQ-Medical	24.2 (5.9)	25.0 (5.7)	22.8 (5.8)	24.6 (6.3)	0.32
FPQ-Severe	34.4 (6.3)	35.2 (6.3)	35.0 (7.0)	33.1 (5.3)	0.38
STAI-S	31.3 (9.1)	30.2 (8.0)	30.5 (6.2)	33.2 (12.1)	0.36
STAI-T	34.9 (8.3)	34.2 (7.4)	34.8 (7.6)	35.9 (9.8)	0.72
TSK-13	22.5 (4.9)	23.01 (4.7)	22.4 (4.8)	22.1 (5.2)	0.72
PCS Total	14.8 (9.1)	15.8 (8.4)	14.4 (10.7)	14.2 (8.4)	0.76
PCS-Rumination	6.5 (4.2)	7.3 (4.0)	6.2 (4.7)	5.9 (3.7)	0.43
PCS-Magnification	2.9 (2.2)	2.8 (1.9)	3.0 (2.4)	3.1 (2.2)	0.84
PCS-Helplessness	5.4 (4.0)	5.8 (3.7)	5.2 (4.7)	5.2 (3.7)	0.80
Race/Ethnicity					0.22
Caucasian	64	26	18	20	
African American	6	1	2	3	
Asian	12	4	4	4	
Hispanic	5	1	2	2	

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Variable	Sample (N=92)	SMT (N=32)	MOB (N = 30)	REST (N = 30)	p-value post-randomization differences
American Indian	1	0	0	1	
Other	4	0	4	0	
Education	16.1 (1.8)	16.2 (1.6)	15.7 (1.3)	16.4 (2.5)	0.29
Smoking Status	1 (1%)	1 (3%)	0 (0%)	0 (0%)	0.40
Rating Most Painful Event Experienced	64.1 (18.4)	68.5 (13.7)	65 (22.1)	66.5 (19.4)	0.76
Rating Most Painful event Imaginable	96.0 (6.6)	97.6 (3.8)	93.8 (8.7)	96.4 (6.1)	0.07

Table 2

ANOVA Summary

Measure: TSP Leg	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Source						
Intercept	3.074	1	3.07	1.00	0.32	0.01
Time	0.12	1	0.12	0.09	0.77	0.00
Group	5.12	2	2.56	0.84	0.44	0.02
Group*Time	9.40	2	4.7	3.45	0.03	0.08

Table 3

Effect Sizes Cohen's d

	SMT vs MOB	SMT vs REST	MOB vs REST
Primary Analysis	−0.07	−0.73	−0.636
Sub Analysis: Facilitatory Cluster	0.168	0.707	0.268
Sub Analysis: No Change Cluster	0.686	−0.577	−1.086
Sub Analysis: Inhibitory Cluster	−2.128	−6.208	−1.728

Table 4

Agglomeration Coefficient Analysis (Average Arm + Leg TS)

Number of Clusters after combining	Coefficient Previous Step	Coefficient This Step	Change	% Change in Heterogeneity
8	35.0	30.0	5.0	14.3%
7	42.5	35.0	7.5	17.6%
6	50.1	42.5	7.6	15.2%
5	60.0	50.1	9.9	16.5%
4	80.4	60.0	20.4	25.4%
3	116.9	80.4	36.5	31.2%
2	182.0	116.9	65.1	35.8%
1		182.0		

Table 5

Baseline Characteristics of TSP clusters

Variable	No TS (N=48)	TS (N = 24)	TD (N = 20)	p-value cluster differences
Gender	32.3%	12.5%	30.0%	0.22
Age	24.1 (5.5)	23.1 (5.4)	24.0 (5.1)	0.76
H-Thres Arm	45.2 (2.7)	44.0 (3.2)	45.8 (2.1)	0.09
P-Thres Arm	24.7 (12.2)	25.0 (9.1)	24.9 (7.6)	0.99
H-Thres Leg	45.2 (3.0)	45.0 (1.9)	46.4 (2.0)	0.16
P-Thres Leg	33.2 (14.9)	32.5 (11.0)	32.2 (7.9)	0.95
TS Intercept Arm	37.3 (24.8)	44.9 (25.0)	46.7 (24.2)	0.26
TS Slope Arm	-0.42 (1.6)	0.34 (1.5)	-1.02 (1.7)	0.01*
TS Intercept Leg	25.6 (20.9)	29.0 (17.7)	38.8 (18.7)	0.05*
TS Slope Leg	0.08 (0.4)	1.92 (1.0)	-1.82 (0.8)	0.00*
FPQ Total	73.0 (14.5)	83.2 (11.9)	77.4 (13.4)	0.01*
FPQ-Minor	17.4 (4.6)	19.5 (4.4)	17.7 (4.7)	0.15
FPQ-Medical	22.87 (5.9)	26.5 (5.5)	24.6 (5.8)	0.04*
FPQ-Severe	32.8 (6.6)	37.1 (5.5)	35.2 (5.2)	0.02*
STAI-S	30.0 (7.8)	32.3 (9.7)	33.2 (11.2)	0.35
STAI-T	34.5 (7.9)	34.6 (8.3)	36.5 (9.4)	0.66
TSK-13	22.4 (4.5)	22.5 (4.8)	23.0 (5.9)	0.89
PCS Total	14.4 (9.7)	15.1 (7.8)	15.4 (9.7)	0.91
PCS-Rumination	6.4 (4.1)	6.5 (4.1)	6.8 (4.4)	0.93
PCS-Magnification	2.7 (2.3)	2.8 (1.7)	3.6 (4.4)	0.28
PCS-Helplessness	5.3 (4.5)	5.8 (3.4)	5.0 (3.5)	0.78
Race/Ethnicity				0.40
Education	17.9 (1.2)	15.4 (0.8)	16.5 (1.5)	0.51
Smoking Status	1 (2%)	0 (0%)	0 (0%)	0.64
Rating Most Painful	65.2 (21.5)	65.0 (20.1)	60.0 (25.8)	0.67
Event Experienced				
Rating Most Painful event Imaginable	96.5 (5.8)	95.4(8.0)	95.5 (6.8)	0.76
TREATMENT GROUPs				0.16
SMT	12	15	5	
MOB	8	17	5	
REST	4	16	10	

Table 6

ANOVA Summary

Measure: TSP Leg	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Source						
Intercept	0.01	1	0.01	0.01	0.94	0.00
Time	0.12	1	0.12	0.01	0.92	0.00
Group	1.82	2	0.91	0.80	0.45	0.02
Cluster	135.36	2	67.68	59.52	0.00	0.60
Time*Group	3.68	2	1.84	1.76	0.18	0.04
Time*Cluster	19.10	2	9.55	9.11	0.00	0.19
Group*Cluster	13.68	4	3.42	3.00	0.02	0.13
Time*Group*Cluster	10.56	4	2.64	2.52	0.04	0.12